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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,946	08/09/2005	Bernard Pau	263432US0XPCT	4965
22850 7590 10/13/2009 OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314				
EXAMINER AEDER, SEANE				
ART UNIT		PAPER NUMBER		
1642				
NOTIFICATION DATE		DELIVERY MODE		
10/13/2009		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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**Advisory Action
Before the Filing of an Appeal Brief**

Application No. 10/516,946	Applicant(s) PAU ET AL.
Examiner SEAN E. AEDER	Art Unit 1642

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 October 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
 Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) ☐ They raise the issue of new matter (see NOTE below);
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
 5. ☐ Applicant's reply has overcome the following rejection(s): _____.
 6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
 The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: _____.
 Claim(s) objected to: _____.
 Claim(s) rejected: 1, 2, 5, 8, 10-12, 24 and 27.
 Claim(s) withdrawn from consideration: 6, 7, 9, 13 and 19-23.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
 13. ☐ Other: _____.

/Sean E Aeder/
Primary Examiner, Art Unit 1642

Continuation of 11, does NOT place the application in condition for allowance because: Claims 1, 2, 5, 8, 10, 12, 24, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828), for the reasons stated in the Office Action of 5/23/08, for the reasons stated in the Office Action of 2/2/09, and for the reasons set forth below.

Maurer et al teaches a process comprising measuring the level of mRNA encoding Bax by detecting expression of an effector or marker gene expressing the pro-apoptotic Bax protein in a colorectal cancer cell from a subject having colorectal cancer, comprising detecting mRNA transcripts, wherein a probe or primer is used to detect the expression of the Bax gene, comprising contacting a nucleotide probe for said effector or marker gene with a biological sample to be analyzed for a time and under conditions suitable for hybridization to occur and detecting hybridization (see Figure 2, in particular). Maurer et al further teaches expression of the BAX gene varies in colorectal cancer cells (see Figure 2, in particular).

Maurer et al does not specifically teach methods comprising determining the level of expression of BAX gene in cancer cells obtained from a patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin. However, these deficiencies are made up in the teachings of Macpherson et al and Chao et al.

Macpherson et al teaches reduced expression of Bcl-xl in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract).

Chao et al teaches Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX (page 821 and page 826, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with an inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic factor of Bcl-xl is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown inhibited by a reduction in expression of Bcl-xl, Bcl-xl functions as a repressor of apoptosis by heterodimerizing with an inhibiting pro-apoptotic BAX, and the pro-apoptotic function of BAX would be diminished in colorectal cancer cells with lower levels of BAX that were treated with oxaliplatin (just as the anti-apoptotic factor of Bcl-xl is diminished in colorectal cancer cells with lower Bcl-xl expression treated with oxaliplatin). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

The amendments to the claims and the arguments found in the Reply of 10/5/09 have been carefully considered, but are not deemed persuasive. In regards to the argument that the prior art does not disclose or suggest all the elements of the invention, the invention is rendered obvious by the prior art for the reasons above. In regards to the argument that the Office Action does not articulate why the invention would be obvious to one of skill in the art at the time of the invention, the reasons why the invention would be obvious to one of skill in the art at the time of invention are discussed above. It is acknowledged that Macpherson and Chao do not concern detecting differences between Bax and Bcl expression in tumor and control cells. In regards to the argument that none of the cited documents suggest that oxaliplatin resistance correlates with Bax gene expression, correlation of Bax gene expression with oxaliplatin resistance is rendered obvious for the reasons stated above. In regards to the argument that Macpherson does not suggest comparing the level of expression of the gene encoding Bcl-xl in tumor and control cells to determine the degree of oxaliplatin resistance, Macpherson teaches decreased expression of Bcl-xl in tumor cell (Bcl-xl ko cells) as compared to control cells resulted in enhanced apoptotic response and attributed that apoptotic response to a BAX:Bcl-xl ratio. In regards to the argument that in view of Chao the person of ordinary skill would have used the ratio of the pair Bcl-2/Bax compared to unbound Bax than the level of Bax alone, this rejection is not based solely on Chao and reasons why it is obvious to use levels of Bax are discussed above. In regards to the argument that Chao is silent about whether Bax gene expression alone correlates with resistance, the rejection is not based solely on Chao. Further, a method comprising determining the ratio of the pair Bcl-2/Bax as compared to unbound Bax in cancer and oxaliplatin resistant cells requires detecting the expression of Bax in cancer and oxaliplatin resistant cells and comparing expression of Bax in cancer and oxaliplatin resistant cells. Such a method anticipates the claims. In regards to the argument that if the level of expression of Bax is high and the level of expression of Bcl-xl is high all Bax proteins would be heterodimerized and inhibited and there would be no decrease in oxaliplatin resistance despite high level of Bax, a high

level of Bax would "indicate" that a cancer cell is not resistant to oxaliplatin as claimed. In regards to the argument that weak levels of Bax are not necessarily correlated with an enhanced resistance to oxaliplatin, weak levels of Bax would "indicate" that a cancer cell is resistant to oxaliplatin as claimed. In regards to the argument that none of the cited documents suggest that in cancer cells the level of Bax taken alone is indicative of oxaliplatin resistance or "wherein reduced expression of said effector or marker gene in said cancer cell compared to said control cell indicates that said cancer cell is resistant to oxaliplatin", the claimed invention is obvious for the reasons stated above. Further, the claims do not limit one to only use the level of Bax or Bak to determine oxaliplatin resistance. Rather, the claims are drawn to methods "comprising" using the level of Bax or Bak to determine oxaliplatin resistance.

Claims 1, 2, 5, 8, 10-12, 24, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828) as applied to claims 1, 2, 5, 8, 10, 12, 24, and 27 above, and further in view of Aggarwal et al (J Immunol, February 1998, 160(4): 1627-1637) for the reasons stated in the Office Action of 2/2/09 and for the reasons set-forth below.

The combined teaching Maurer et al, Macpherson et al, and Chao et al are discussed above.

The combined teachings of Maurer et al, Macpherson et al, and Chao et al do not specifically teach a method comprising obtaining a cDNA from the RNA of the biological sample and amplifying the cDNA using at least one primer for amplification of BAX. However, this deficiency is made up in the teachings of Aggarwal et al.

Aggarwal et al teaches a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX (Figure 7, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined method of Maurer et al, Macpherson et al, and Chao et al because the quantitative PCR method of Aggarwal et al would provide quantitative results for determining BAX expression in the combined method of Maurer et al, Macpherson et al, and Chao et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined method of Maurer et al, Macpherson et al, and Chao et al because Aggarwal et al teaches primers that amplify BAX cDNA and methods of using said primers to amplify BAX cDNA (page 1628, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 10/5/09, Applicant states that Chao et al does not remedy alleged deficiencies which have been addressed above.